Aus der
Abteilung für
Handchirurgie, Plastische Chirurgie und Ästhetische Chirurgie
Klinik der Universität München

Understanding the shape and motion behavior of the forehead

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von
Konstantin Frank

Jahr der mündlichen Prüfung : 2022

Aus der
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Vorstand: Prof. Dr. Riccardo E. Giunta

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aus
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2022

Mit Genehmigung der Medizinischen Fakultät
der Universität München

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Tag der mündlichen Prüfung:	05.05.2022

Eidesstattliche Versicherung

Ich erkläre hiermit an Eides statt, dass ich die hier vorliegende Dissertation mit dem Thema:

Understanding the shape and motion behavior of forehead lines

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Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

München, 01.09.2019 Dr. med. univ. Konstantin Frank

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Rot markiert = Für kumulative Dissertation relevante Publikationen

Bestätigung der Ko – Autoren

Siehe Anlage I + II

Der Doktorand, Herr Konstantin Frank, der in der ersten Publikation als Co – Autor und bei der zweiten Publikation als Erstautor auftritt, hat das Thema der Dissertation sowie den Studienaufbau gemeinsam mit Herrn Prof. Dr. Dr. Thilo L. Schenck und Prof. Sebastian Cotofana entwickelt. Vorbereitungen, wie die Probandenakquise, Datenerfassung anhand objektiver Messmethoden und die statistische Auswertung der Studiendaten, erfolgten eigenständig. Beide Publikationen wurden zunächst eigenständig durch den Doktoranden, Herrn Konstantin Frank, verfasst und anschließend durch Herrn Prof. Dr. Dr. Thilo L. Schenck und Prof. Sebastian Cotofana korrigiert und schließlich in eigenständiger Arbeit in ihre endgültigen Fassungen gebracht.

Weder die vorliegende kumulative Dissertation, noch die angegebenen Publikationen sind Bestandteil einer anderen (laufenden oder abgeschlossenen) Dissertation der Doktorandin oder eines Ko-Autors.

Einleitung

Im Jahre 2018 wurden in den USA insgesamt ca. 7.5 Millionen Behandlungen mit neuromodulatorischen Toxinen für ästhetische Zwecke durchgeführt. Alleine in Deutschland haben sich mehr als 300.000 Patienten einer Behandlung mit neuromodulatorischen Toxinen unterzogen.[1]

Professor Emilie Pierre van Ermengem identifizierte im Jahre 1895 ein Toxin, welches von dem Bakterium Clostridium botulinum produziert wird und vorrangig für Lebensmittelvergiftung verantwortlich ist und nannte es Botulinumtoxin.[2] 24 Jahre später, 1919, etablierte Professor Burke eine Klassifikation der verschiedenen Botulinumtoxin – Stränge, basierend auf den Erkenntnissen von Prof. van Ermengem. Im letzten Jahrhundert führten weitreichende Untersuchungen zur Identifikation von sieben verschiedenen Botulinumtoxin Strängen: namentlich Botulinumtoxin A-G.[3] 1920 konnte durch Dr. Herman Sommer erstmalig Botulinumtoxin A isoliert werden.[4] Nach zwei Jahren intensiver Arbeit konnte die Arbeitsgruppe von Dr. Edward Schantz im Jahre 1946 ein gereinigtes, in kristalliner Form vorliegendes Botulinumtoxin A isolieren.[5,6] Dr. Vernon Brook zeigte im folgenden Jahrzehnt, dass der Mechanismus von Botulinumtoxin A auf der Blockade der Freilassung von Acetylcholin an der motorischen Endplatte beruht. [5,6] Die Smith – Kettlewell Eye Research Foundation begann in den 60er Jahren mit der Erforschung des klinischen Einsatzes von Botulinumtoxin in der Behandlung von Strabismus.[7] 1980 zeigten Scott et al., dass eine Injektion von Botulinumtoxin A eine sensitive Schwächung der extraokulären Muskulatur erlaubt und Strabismus effektiv behandeln kann.[8]

Botulinumtoxin, unabhängig vom Strang, besteht aus neurotoxischen Komponenten: einer leichten (50 kDa) und einer schweren Kette (100 kDa), welche über eine einfache di-sulphit Bindung verbunden sind, sowie aus nicht – neurotoxischen Komponenten (Haemagglutinin Komplex mit 60 kDa und nicht-haemagglutinierenden Proteinen mit 130 kDa).[9] Sobald ein Aktionspotential das terminale Axon eines Nervens an der motorischen Endplatte depolarisiert, kommt es zur Freilassung von

Acetylcholin in den synaptischen Spalt. Die Ausschüttung von Acetylcholin wird durch ein Transportprotein durchgeführt (soluble N-ethyl-maleimide-sensitive factor attachment protein receptor, SNARE). Die schwere Kette des neurotoxischen Bestandteils von Botulinumtoxin bindet an einem spezifischen Glykoprotein. In der daraufhin folgenden intrazellulären Internalisierung des Toxins verbindet sich die leichte Kette des neurotoxischen Bestandteils von Botulinumtoxin mit dem SNARE Komplex. Die Zielproteine, an welche die leichte Kette bindet, variiert zwischen den verschiedenen Strängen des Botulinumtoxin. Durch eine proteolytische Spaltung des SNARE Komplexes verhindert Botulinumtoxin eine Bindung und Fusion des freigelassenen Acetylcholins an der inneren Membran und führt somit in Muskelzellen zu einer chemischen Denervation und in exokrinen Schweißdrüsen zu einer Blockade der glandulären Sekretion. Die Reversibilität von Botulinumtoxin erklärt sich durch die Synthese neuer SNARE Proteine, an welchen keine proteolytische Spaltung des Botulinumtoxin stattfindet.[9,10]

Von der FDA zugelassene neuromodulatorische Toxine, im Volksmund oftmals als Botox bezeichnet, sind Abobotulinumtoxin A, Incobotulinumtoxin A, Onabotulinumtoxin A und Rimabotulinumtoxin B, welche sich durch ihre pharmakologischen Eigenschaften unterscheiden.[9] Seit der Einführung von neuromodulatorischen Toxinen in ersten Studien Anfang der 90er Jahre hat sich die Perzeption einer Behandlung mit Neurotoxinen von einer ablehnenden, oftmals zurückhaltenden zu einer alltäglichen, weitverbreiteten und gesellschaftlich akzeptierten Behandlungsform entwickelt, was sich in den jährlich steigenden Zahlen von Botox – Behandlungen wiederspiegelt.[11,12] Der historische Ursprung in der Anwendung von neuromodulatorischen Toxinen findet sich in der Behandlung von Krankheitsbildern mit muskulärer Hyperaktivität, vor allem fokaler Dystonien.[2] Nach Jahren der Anwendung von Neuromodulatoren in Patienten mit fokalen Dystonien im Gesicht, welche den Patienten eine maßgebliche Steigerung der Lebensqualität erbrachte, erkannten Jean und Alastair Carruthers Anfang der 90er Jahre das Potential von Neurotoxinen in der Behandlung von Gesichtsfalte, welche durch muskuläre Hyperaktivität entstanden sind und etablierten diese Behandlungsmethode durch zahlreiche Studien vorranging in der ästhetischen Dermatologie und der plastischen Chirurgie.

Neben der Behandlung von unerwünschten Gesichtsfalten konnte der Einsatz von Neuromodulatoren maßgebliche Besserung der Beschwerden von Migräne – Patienten erwirken.[12]

Eine der häufigsten Lokalisierungen für die Anwendung von Neurotoxinen zur Faltenbekämpfung ist die Stirn.[13] Eine glatte Stirn wird oftmals mit Jugendlichkeit, Zufriedenheit und Sorglosigkeit assoziiert.[14] Injektionen von Botulinomtoxin in der Stirn weisen eine hohe Patientenzufriedenheit bei gleichzeitig geringen Nebenwirkungen auf. Klassische Nebenwirkungen von Injektionen in den Musculus frontalis ist eine Augenlidptose, ein asymmetrisches Ergebnis oder eine Hypohidrose.[15]

In einer von 2016 von Sundaram et al. veröffentlichten Leitlinie wird empfohlen, bei der Behandlung von Gesichtsfalten spezifisch die Areale eines Muskels zu adressieren, welche relativ für die größte Hyperaktivität verantwortlich sind. Gleichzeitig wurde die Berücksichtigung demographischer Merkmale, individueller Muskelanatomie und Muskelkontraktionsmuster empfohlen.[15] Bezogen auf Injektionen von Neuromodulatoren in die Stirn sollte sich der praktizierende Arzt somit der Biodynamik des Musculus frontalis, sowie den synergistischen Einflüssen von Alter, Geschlecht und Ethnizität, sowie Einfluss anderer Gesichtsmuskeln auf die Faltenbildung der Stirn bewusst sein, um einen individualisierten und optimierten Plan bei der Behandlung von Stirnfalten entwerfen zu können.[15] In der Literatur finden sich wenige Beschreibungen der makroskopischen und mikroskopischen Anatomie des Musculus frontalis. Kontraktionsmuster des Musculus frontalis sind bis zum heutigen Zeitpunkt noch nicht beschrieben worden.

Der erste Teil dieser kumulativen Dissertation Ziel untersucht den Zusammenhang zwischen der Bewegung der Stirnhaut und der Formgebung der horizontalen Stirnfalten, während der zweite Teil sich mit dem Bewegungsmuster der Stirnhaut während des aktiven Stirnrunzelns befasst. Zielsetzung beider Arbeiten ist es anhand klinisch sichtbarer morphologischer Eigenschaften ein präziseres, auf den Patienten individuell zugeschnittenes Injektionsmuster bei Behandlungen mit Botulinumtoxin zu ermöglichen.

Der erste Teil der Studie umfasste 37 gesunde Probanden (29 Kaukasier, 6 Afroamerikaner, 2 Asiaten) mit einem Durchschnittsalter von 39.84 ± 14.4 Jahren [22- 73]. Freiwillige Teilnehmer wurden gescreent und ausgeschlossen, wenn frühere minimalinvasive Injektionen von Neuromodulatoren, gesichtschirurgische Eingriffe, Trauma oder Krankheiten die Integrität der Gesichtsanatomie beeinträchtigten oder die Funktion des Musculus frontalis beeinflussen konnten. Die Probanden wurden über die Ziele, den Umfang und das Verfahren der Studie unterrichtet, und jeder Teilnehmer erteilte vor Beginn der Studie eine schriftliche Einwilligung zur Verwendung seiner Daten und der dazugehörigen Bilder. Die Studie wurde von der Ethikkomission der Ludwig-Maximilians-Universität München genehmigt (Protokollnummer: 266-13). Diese Studie wurde in Übereinstimmung mit den regionalen Gesetzen (Deutschland) und der guten klinischen Praxis durchgeführt.

Unter Verwendung eines Vectra H1-Kamerasystems (Canfield Scientific Inc., Fairfield, New Jersey, USA) wurden 3D-Bilder der kompletten Gesichter der Probanden erstellt. Zwei aufeinanderfolgende Bilder wurden in Ruhe (Baseline Scan) und bei maximaler Brauenhöhe / Frontalis-Kontraktion (Follow-up Scan) aufgenommen. Jeder Follow-up Scan wurde auf seinen jeweiligen Baseline Scan synchronisiert, um Unterschiede in der Hautposition zu berechnen und so Hautverschiebungsvektoren zu berechnen. Eine maximale mittlere Oberflächenabweichung bei der Überlagerung des Baseline und Follow – Up Scans von 0.1 mm wurde toleriert. Mit dem automatisierten Algorithmus der Vectra Software Suite® (Canfield Scientific Inc., Fairfield, New Jersey, USA) wurden x- und y- Werte für die lokalen Veränderungen der Hautposition berechnet und visualisiert. Die Berechnung der x- und y- Werte basiert auf der Erkennung der Verschiebung von Hautporen, welche durch die H2 Kamera und die dazugehörige Software erkannt und synchronisiert werden können.

Horizontale Stirnfalten wurden dichotom in gerade oder gewellte Stirnfalten eingeteilt. Wellenförmige Stirnfalten waren durch eine undulierende Ausrichtung (vergleichbar mit einer Welle) gekennzeichnet, während gerade Stirnfalten durch eine horizontale, gleichmäßige Ausrichtung (parallel zu den

Augenbrauen) gekennzeichnet waren. Die Länge und Richtung des Hautverschiebungsvektors wurde mit dem automatisierten Algorithmus der Vectra Software Suite® berechnet. Der Winkel zwischen der vertikalen (kranio-kaudalen) Achse des durch die Pupille verlaufenden Gesichts (= vertikale Mittellinie) und der Richtung des mittleren Hautverschiebungsvektors (= mittlerer Stirnbewegungswinkel) wurde erhoben.

Die Beziehung zwischen der Form der Stirnfalten (gerade und gewellte Falten) und dem Alter, dem Geschlecht und dem mittleren Stirnbewegungswinkel wurde mithilfe von Chi-Quadrat Test, Student's T-Test und Pearson's Korrelationsanalysen berechnet. Alle statistischen Analysen wurden mit SPSS Statistics 25 (IBM, Armonk, NY, USA) durchgeführt, und die Ergebnisse wurden ab $p \leq 0.05$ als statistisch signifikant eingestuft.

Es zeigte sich bei 21 Probanden (8 Männer, 13 Frauen) eine gerade Stirnfalte, während 16 Probanden (10 Männer, 6 Frauen) gewellte Stirnfalten aufwiesen. Der mittlere Stirnbewegungswinkel betrug insgesamt 13.19 ± 8.6 °; zwischen Männern (14.36 ° ± 8.7) und Frauen (12.03 ° ± 8.4) zeigte sich hier kein statistisch signifikanter Unterschied ($p = 0.250$). Der mittlere Stirnbewegungswinkel auf der rechten Seite betrug 13.67 ° ± 9.5 und auf der linken Seite 12.72 ° ± 7.6 ($p = 0.643$).

Der mittlere Stirnbewegungswinkel war für Probanden mit einer geraden horizontalen Stirnlinie 6.68 ° ± 2.9 [0.0 – 12.0], während der mittlere Stirnbewegungswinkel für Probanden mit gewellten horizontalen Stirnfalten 21.34 ° ± 5.9 [11.0 – 37.0] betrug ($p < 0.001$). Dieser statistisch signifikante Unterschied zeigte sich ebenfalls, wenn zusätzlich noch geschlechterspezifisch analysiert wurde: Männer: 6.13 ° ± 2.8 [0.0 – 11.0] vs. 20.95 ° ± 5.5 [11.0 – 32-0] ($p <0.001$); Frauen: 7.04 ° ± 2.9 [0.0 - 12.0] vs. 22.00 ° ± 6.6 [11.0 - 37.0] ($p <0.001$)).

Unabhängig vom Geschlecht unterschieden sich junge Probanden (Alter unter 40 Jahre) nicht in ihrem mittleren Stirnbewegungswinkel im Vergleich zu älteren Probanden (Alter über 40 Jahre). Dies zeigte sich sowohl bei Männern (14.92 ° ± 9.2 vs. 13.25 ° ± 7.7 ($p = 0.595$)), als auch bei Frauen (12.25 ° ± 8.6 vs. 11.75 ° ± 8.4 (($p = 0.862$)). Zunehmendes Alter korrelierte nicht statistisch signifikant mit einem größeren Stirnbewegungswinkel ($r_p = -0.104$; $p = 0.386$).

Im ersten Teil der Dissertation wurde die Beziehung zwischen der Bewegung der Stirnhaut und der Form horizontaler Stirnfalten mithilfe einer 3D-Analyse der Hautvektorverschiebung untersucht. Unsere Ergebnisse zeigten, dass unabhängig von Alter oder Geschlecht ein größerer Stirnbewegungswinkel mit gewellten Stirnfalten von 21.34 ° ± 5.9 mit ($p <0.001$) korrelierte, während gerade Stirnfalten mit einem kleineren Stirnbewegungswinkel von 6.68 ° ± 2.9 ($p <0.001$) korrelierten. Junge Probanden (<39.8 Jahre) unterschieden sich im Vergleich zu älteren Probanden (> 39.8 Jahre) nicht in ihrem mittleren Stirnbewegungswinkel: 13.70 ° ± 9.0 gegenüber 12.39 ° ± 8.0 mit $p = 0.530$. Es wurden keine Unterschiede zwischen der rechten und linken Stirnseite mit $p = 0.944$ beobachtet.

3D-Analysen zeigen, dass gewellte Stirnfalten signifikant mit einem größeren Stirnbewegungswinkel assoziiert sind, während gerade horizontale Stirnfalten mit einem kleineren Stirnbewegungswinkel assoziiert sind. Die Bewegung der Haut an der Stirn kann als Ergebnis einer mehrschichtigen Reaktion des Weichgewebes auf die zugrunde liegende Muskelkontraktion verstanden werden. Die Frontalis-Muskelkontraktion wird über kurze Septae, auch Retinaculae cutis genannt, auf die Dermis übertragen. Diese Bewegungsübertragung wird durch die Dicke des oberflächlichen Unterhautfetts beeinflusst, das sich in den drei oberflächlichen Stirnfettkompartimenten befindet[14,16], und es kann angenommen werden, dass eine dickere Fettschicht zu einer abgeschwächten Hautbewegung führt. Ebenso kann eine erhöhte Septumlaxität zu einer verminderten Bewegung der Stirnhaut führen, da die Kraftübertragung zwischen dem Musculus frontalis und der Dermis verringert ist.

Die Ergebnisse der vorliegenden Studie zeigen, dass bei gewellten horizontalen Stirnfalten eine eher lateral ausgerichtete Bewegung der Stirnhaut auftritt, während mit geraden horizontalen Stirnfalten eine eher zentral ausgerichtete Bewegung zu beobachten ist. Die Ergebnisse unterstützen die Resultate einer vorherigen anatomischen Studie unserer Forschungsgruppe. Moqadam et al. konnten in einer 2017 veröffentlichten Publikation aufzeigen, dass ein größerer Winkel der Muskelfasern in Relation zur Mittellinie der Stirn mit undulierenden Stirnfalten einhergeht, während ein kleinerer Winkel der Muskelfasern mit horizontal verlaufenden Stirnfalten korreliert.[17] Basierend auf der Hypothese, dass muskulär bedingte Falten im Gesicht sich immer perpendikulär zur Muskelbewegung bilden ist dies verständlich. Da die Studie jedoch Präparate – basiert durchgeführt wurde kann die vorliegende klinische Studie als realitätsnähere Fortsetzung angesehen werden. Für den behandelnden Arzt ist somit zu beachten, dass Patienten mit undulierenden Stirnfalten ein lateral orientiertes Injektionsmuster benötigen, um auch den Zug der nach außen orientierten Fasern des M. frontalis zu unterbinden und ein homogenes Resultat zu erzielen. Beachtet man die klinische Formgebung der Stirnfalten nicht, kann es zu einer unerwünschten Kontraktion der lateralen Fasern bei gleichzeitig gelähmten medialen Fasern des M. frontalis kommen und eine permanent angehobene Augenbraue kommen, was dem Patienten oftmals einen kritischen Gesichtsausdruck verleiht. Zusammenfassend lässt sich festhalten, dass undulierende Stirnfalten Injektionspunkte, die lateraler angeordnet sind, erfordern, während parallel verlaufende Falten zentraler angeordnete Injektionspunkte erfordern.

Die zweite, zu dieser kumulativen Dissertation gehörige Publikation beschäftigt sich mit dem erweiterten, kranio-kaudal orientierten Kontraktionsmuster der Stirn und potentiellen Auswirkungen auf minimal-invasive Behandlungen mit Neuromodulatoren. Eine oftmals und unliebsame Erscheinung nach der Injektion von Neuromodulatoren ist eine Ptosis der Augenbrauen und des Augenlides. Ist eine Ptosis des Augenlides oftmals durch eine lateral zu tiefe Injektion und eine Diffusion des Neurotoxins entlang des supraorbitalen Gefäß-Nervenbündel Kanals in den M. levator palpaebrae zu erklären, ist bisher kein wissenschaftlich fundierter Erklärungsansatz für die Hypothese und klinische Beobachtung, dass eine zu kaudal lokalisierte Injektion von Neurotoxinen zur einer Ptosis der Augenbrauen führen kann in der Literatur zu finden.

Der zweite Teil der Studie umfasste 27 gesunde Probanden (14 Kaukasier, vier Afroamerikaner, drei Asiaten und sechs Probanden fernöstlicher Abstammung) mit einem Durchschnittsalter von 37.50 ± 13.7 Jahren [22- 73]. Freiwillige Teilnehmer wurden gescreent und ausgeschlossen, wenn frühere minimalinvasive Injektionen von Neuromodulatoren, gesichtschirurgische Eingriffe, Trauma oder Krankheiten die Integrität der Gesichtsanatomie beeinträchtigten oder die Funktion des Musculus frontalis beeinflussen konnten. Zudem wurden Probanden ausgeschlossen, wenn kein eindeutiger Haaransatz identifiziert werden konnte. Die Probanden wurden über die Ziele und den Umfang der Studie unterrichtet. Jeder Teilnehmer erteilte vor Beginn der Studie eine schriftliche Einwilligung zur Verwendung seiner Daten und der dazugehörigen Bilder. Die Studie wurde von der Ethikkomission der Ludwig-Maximilians-Universität München genehmigt (Protokollnummer: 266-13). Diese Studie wurde in Übereinstimmung mit den regionalen Gesetzen (Deutschland) und der guten klinischen Praxis durchgeführt.

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Ausrichtung und Stärke der Hautverschiebungsvektoren wurden erhoben. Basierend auf jenen Hautverschiebungsvektoren wurde Hautkompression (prozentuelle Reduktion der Stirnlänge) und Hautverschiebung (in mm) berechnet. Stirnhöhe, Entfernung zwischen Augenbraue und Konvergenzlinie des M. frontalis wurden mittels Shapiro – Wilk Test auf eine Normalverteilung geprüft. Geschlechtsspezifische Unterschiede wurden mittels Student's T – Test berechnet. Unterschiede zwischen den verschiedenen Ethnizitäten wurden mittels multivariater Analyse berechnet. Alle statistischen Analysen wurden mit SPSS Statistics 25 (IBM, Armonk, NY, USA) durchgeführt, und die Ergebnisse wurden ab $p \leq 0.05$ als statistisch signifikant eingestuft.

Die durchschnittliche Stirnlänge, definiert als die Distanz zwischen oberer Augenbraue und Haaransatz, betrug 65.0 ± 8.1 mm bei Männern und 53.4 ± 9.2 mm bei Frauen ($p = 0.002$). Innerhalb der vier Ethnizitäten zeigte sich kein statistisch signifikanter Unterschied der Stirnlänge ($p = 0.565$). In allen untersuchten Probanden (100%) zeigte sich eine bimodale Bewegung des M. frontalis. Die Haut der unteren Stirn bewegte sich kranial, während simultan eine kaudal ausgerichtete Bewegung der oberen Stirn zu beobachten war. Diese bimodale Bewegung resultierte in einer Anhebung der Augenbraue und einer Absenkung des Haaransatzes und in einer, in der Mitte liegenden, starren Zone, welche als Konvergenzlinie (C – Line) bezeichnet wurde. Diese C – Line befand sich bei Männern 39.6 ± 7.7 mm und bei Frauen 34.3 ± 7.3 mm kranial des oberen Randes der Augenbrauen. Auch hier zeigte sich innerhalb der vier Ethnizitäten kein statistisch signifikanter Unterschied ($p = 0.370$). Die mediane Position der Konvergenzlinie (C – Line) konnte an der zweiten horizontal - verlaufenden Stirnfalte (ab der Haargrenze zählend) identifiziert werden.

Der M. frontalis ist der einzige Augenbrauenheber im menschlichen Körper. Antagonisierend arbeiten als Augenbrauensenker der M. Orbicularis oculi, M. Depressor supercilii, M. corrugator supercilii und M. procerus. Eine Reduktion der Kontraktilität des M. frontalis, insbesondere des unteren, nach kranial ziehenden Anteils kann eine potentielle Absenkung der Augenbrauen verursachen. Eine Augenbrauenptosis nach Behandlungen des M. frontalis mit Neurotoxinen ist mit einer Inzidenz von 0.6 – 20% beschrieben.[15] Obwohl die vorliegende Studie keinerlei neuromodulatorischen Injektionen a priori untersucht hat, bestätigt die Studie klinische Observationen. Behandlungen des M. frontalis mit Neurotoxinen im unteren Stirndrittel verursachen oftmals eine Augenbrauenptosis. Da die kranial ziehenden Fasern des einzigen Augenbrauenhebers, des M. frontalis, keine Kontraktion mehr durchführen können kippt die zuvor bestehende Balance zwischen M. frontalis und den Augenbrauensenkern zu Gunsten des M. Orbicularis oculi, M. Depressor supercilii, M. corrugator supercilii und M. procerus. Als Resultat kommt es zu einer Ptosis der Augenbauen. Dies ist die erste Studie die objektive, verlässliche Daten für die klinische Observation, dass Injektionen im unteren Anteil des M. frontalis oftmals zu einer Ptosis der Augenbrauen führen, liefert. Basierend auf den Ergebnissen dieser Studie ist davon auszugehen, dass Injektionen von Neurotoxinen oberhalb der identifizierten Konvergenzlinie zu einer niedrigeren Inzidenz einer Ptosis der Augenbrauen führen könnte.

Da die beiden Studien die selbe Modalität der Untersuchung verwendeten wurde ein übergreifender Ethikantrag verwendet.

Zusammenfassung

Publikation 1: Relationship between Forehead Motion and the Shape of Forehead Lines –
A 3–D Skin Displacement Vector Analysis
Englisches – Abstract

Objective: Injections with neurotoxins into the glabellar region and forehead are performed on a frequent basis using established injection mechanisms. The aim of this study was to investigate the individual skin movement of the forehead and transfer newly gained understanding of observed patterns into the clinical context.

Material and Methods: 37 participants (29 Caucasians, 6 African – American, 2 Asian) with an average age of 39.84 ± 14.4 years [range: 22–73] were enrolled in this investigation. 3 Diensional images of the forehead oft he participants were analyzed utilizing a Vectra H1 camera. Consecutively skin displacement vectors were computed between the non-contracted (i.e. baseline) and the maximally contracted forehead (i.e. follow – up) of the volunteers.

Results: Independent of age or gender a greater angle of forehead motion correlated with the presence of undulating forehead lines 21.34° ± 5.9 with $p < 0.001$, while straight forehead lines correlated with a smaller forehead motion angle 6.68° ± 2.9 $p < 0.001$. Females displayed more frequently straight horizontal forehead line when compared to males: 68.4% vs. 44.4% ($p = 0.037$). No age difference could be observed, as young participants (< 39.8 years) did not differ in their mean forehead motion angle as compared to older volunteers (> 39.8 years): 13.70° ± 9.0 vs. 12.39° ± 8.0 with $p = 0.530$.

Conclusion: Injections of neuromodulators in the forehead need to be individualized by assessing the shape of the horizontal forehead lines and categorizing them into either undulating or straigt. Undulating forehead lines should be injected more laterally whereas straight forehead lines should be injected more centrally.

Deutsches – Abstract

Ziel: Injektionen von Neurotoxinen der Stirn werden häufig mit starren, nicht individualisierten Applikationsschemata durchgeführt. Die vorliegende Studie wurde durchgeführt, um das individuelle Hautbewegungsmuster der Stirn zu identifizieren und Bewegungsmuster mit der zugrundeliegenden Morphologie der Stirn in Beziehung zu setzen.

Material und Methoden: 37 gesunde Probanden (29 Kaukasier, sechs Afroamerikaner, zwei Asiaten) mit einem Durchschnittsalter von 39.84 ± 14.4 Jahren [22–73] wurden in dieser Studie untersucht. 3-D-Bilder der Stirn wurden unter Verwendung eines Vectra H1-Kamerasystems angefertigt und analysiert, wobei Hautverschiebungsvektoren zwischen der entspannten und der maximal kontrahierten Stirn der Probanden berechnet wurden. Der Zusammenhang zwischen der Morphologie der horizontalen Stirnfalten (gerade vs. undulierend) und dem Stirnbewegungsmuster wurde analysiert.

Ergebnisse: Unabhängig von Alter oder Geschlecht korrelierte ein größerer Stirnbewegungswinkel von 21.34 ° ± 5.9 mit undulierenden Stirnfalten $p < 0.001$, während gerade Stirnfalten mit einem kleineren Stirnbewegungswinkel von 6.68 ° ± 2.9 $p < 0.001$ korrelierten. Frauen zeigten häufiger gerade horizontale Stirnlinie als Männer: 68.4% vs. 44.4% ($p = 0.037$). Junge Probanden (<39.8 Jahre) unterschieden sich im Vergleich zu älteren Probanden (> 39.8 Jahre) nicht in ihrem durchschnittlichen Stirnbewegungswinkel: 13.70 ° ± 9.0 gegenüber 12.39 ° ± 8.0 ($p = 0.530$).

Schlussfolgerung: Injektionen von Neuromodulatoren in die Stirn können unter Berücksichtigung der Form der horizontalen Stirnfalten individualisiert werden. Undulierende Falten erfordern Injektionspunkte, die lateraler positioniert sind, während horizontal gerade Falten zentraler angeordnete Injektionspunkte erfordern.

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Relationship between forehead motion and the shape of forehead lines—A 3D skin displacement vector analysis

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Abstract

Objective: Neuromodulator injections of the forehead are often performed using standardized protocols. This study was designed to identify the individual skin motion pattern of the forehead and to relate this pattern to the underlying frontalis muscle morphology to offer guidance for neuromodulator placement.

Material and Methods: Thirty-seven healthy volunteers (29 Caucasians, six African Americans, two Asians) with a mean age of 39.84 ± 14.4 years [range: 22-73] were enrolled. 3D images of the forehead were analyzed using a Vectra H1 camera system computing skin displacement vectors between the noncontracted and the maximally contracted forehead of the volunteers. Relationships between the shape of the horizontal forehead lines (straight vs wavy) and the forehead motion pattern were calculated.

Results: Independent of age or gender, a greater forehead motion angle was associated with the presence of wavy forehead lines 21.34°± 5.9 with $P < 0.001$, whereas straight forehead lines were associated with a smaller forehead motion angle 6.68°± 2.9 $P < 0.001$. Females had more frequently straight horizontal forehead lines versus males: 68.4% vs 44.4% ($P = 0.037$). Young volunteers (<39.8 years) did not differ in their mean forehead motion angle when compared to older volunteers (>39.8 years): 13.70°± 9.0 vs 12.39°± 8.0 with $P = 0.530$.

Conclusion: Injections of neuromodulators in the forehead can be individualized by respecting the shape of the horizontal forehead lines. Wavy lines require injection points that are located more laterally, whereas straight lines require more centrally located injection points.

KEYWORDS

3D Scanning, aesthetics, face, facial anatomy, frontalis muscle, injections, neuromodulators, skin vector displacement

1 | INTRODUCTION

A smooth forehead generally connotes youthfulness and contentment.[1,2] Neuromodulators can be applied to the forehead to decrease or even eliminate wrinkles by decreasing the release of presynaptic neurotransmitters thus inhibiting muscular contraction of the frontalis muscle.[1,3,4] The increasing desire for a wrinkle-free forehead in today's society is reflected in the increasing demand for neuromodulator injections, reported by the American Society of Plastic Surgeons. According to their national plastic surgery statistics 2018, the number of Botulinum Toxin Type A treatments increased by 845% between the years 2000 and 2018 (facial region not specified).[5]

Neuromodulator injections in the forehead are reported to have relatively few adverse events, allowing for predictable outcomes and a high level of patient satisfaction.[6-8] However, to create an aesthetically pleasing effect, physicians need to respect the underlying anatomy of the frontalis muscle to avoid telltale signs of neuromodulators like the "Spock eyebrow" also called "Mephisto sign."

A recent cadaveric study suggested a significant relationship between the morphology of the frontalis muscle and the shape of horizontal forehead lines.[9] Wavy forehead lines (undulated wavy orientation) were related to a greater frontalis muscle fascicle angle and to the presence of an aponeurosis, while straight forehead lines (parallel to the eyebrows) were related to a smaller frontalis muscle fascicle angle and the absence of an aponeurosis.[9] However, no conclusions about the dynamic function of the frontalis muscle, that is, skin motion, could be drawn, as the study was conducted in human body donors.

The relationship between the shape of the horizontal forehead lines and forehead motion is not well characterized. Thus, identifying a relationship between the shape of the horizontal forehead lines and forehead skin motion might help to guide physicians toward individualized injection points thus increasing safety and reducing the rate of adverse events. The aim of the present study was to investigate the relationship between the movement of the forehead skin utilizing state-of-the-art 3D skin vector displacement analyses and relate the measurements to the shape of horizontal forehead lines. Results of this investigation might lead to the formation of more individualized neuromodulator injection schemata.

2 | MATERIAL AND METHODS

2.1 | Study sample

The study enrolled 37 healthy volunteers (29 Caucasians, six African Americans, two Asians) with a mean age of 39.84 ± 14.4 years [range: 22-73]. Volunteers were screened and not included in this analysis if they had ever received facial neuromodulators, facial surgeries, or experienced trauma or diseases that disrupted the integrity of the facial anatomy, specifically the function of the frontalis muscle. Volunteers were briefed on the aims, scope, and procedure of the study, and each participant provided written informed consent for the use of both their data and associated images prior to their inclusion into the study. The study was approved by the Institutional Review Board of Ludwig-Maximilian University Munich (IRB protocol number: 266-13). This study was conducted in accordance with regional laws (Germany) and good clinical practice.

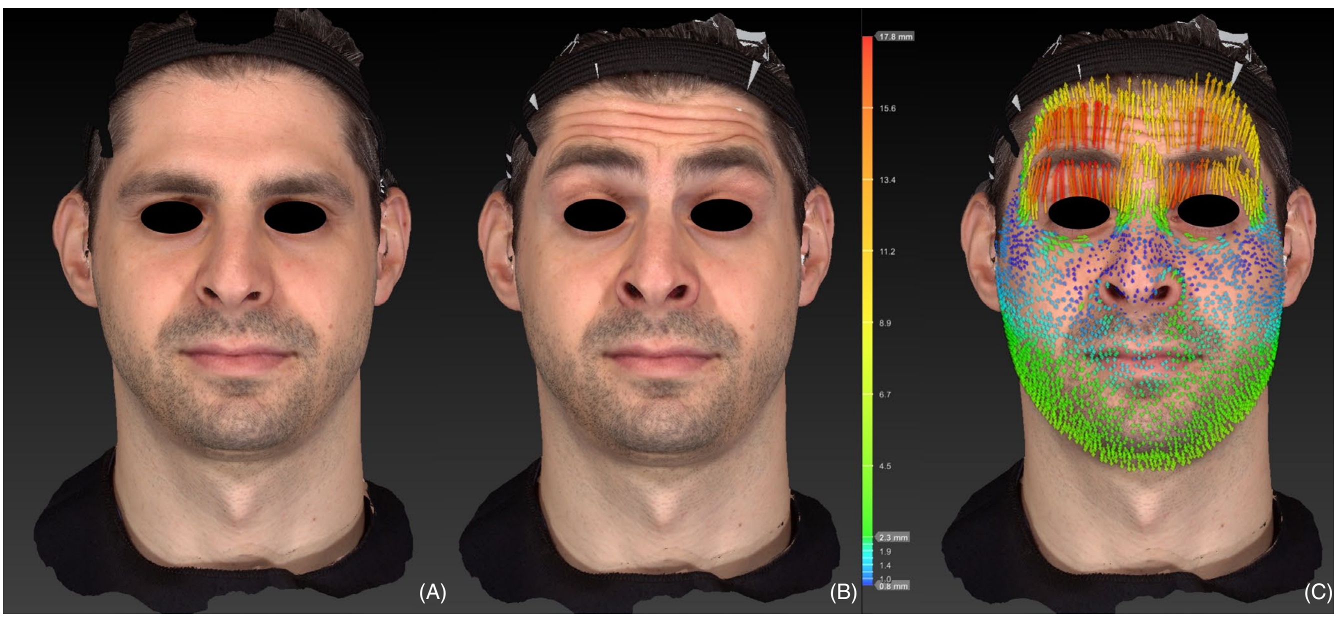

FIGURE 1 Processed 3D scan representing the two different states of the face evaluated in this study and their difference in skin displacement represented through vectors. A, Subject with a relaxed forehead. B, The same subject with a maximal contracted forehead. C, The difference in skin displacement between the pictures A and B, represented through vectors

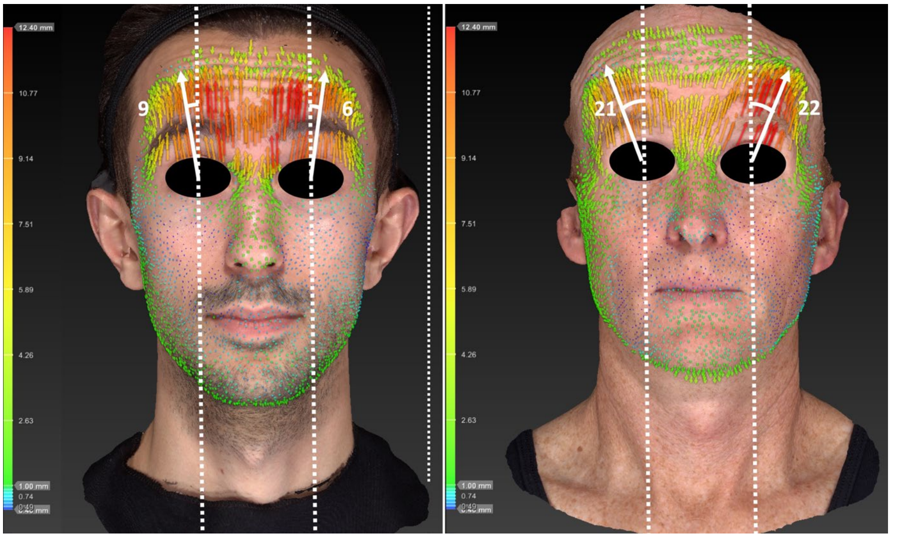

FIGURE 2 Processed 3D scan showing the different angle measurements of a straight forehead (A) and a wavy forehead (B). The measurement of the angle followed the visually evaluated average of the vector direction in the pupillar line above the eyebrow

2.2 | Imaging

3D images of the forehead of the volunteers were obtained utilizing a Vectra H1 camera system (Canfield Scientific Inc). Two consecutive pictures of the forehead of the volunteers were taken at rest (baseline image) and upon maximal frontalis contraction/forehead wrinkling (follow-up image). Each follow-up scan was aligned to its respective baseline scan to compute differences in skin position and thus to calculate skin displacement vectors. Applying the automated algorithm of the Vectra Software Suite®, values for local changes in skin displacement were calculated and visualized (Figure 1). A maximal mean surface deviation of 0.1 mm was tolerated. All surface analytic procedures were conducted by the same investigator (DF).

2.3 | Data analyses

Horizontal forehead lines were classified dichotomously according to a previous publication[9] into straight or wavy forehead lines. Wavy forehead lines were characterized by an undulated orientation, whereas straight forehead lines were characterized by a horizontal even orientation (parallel to the eyebrows).

The length and the direction of the skin displacement vector based on the skin movement of the forehead upon maximal frontalis contraction were calculated by the automated algorithm of the Vectra Software Suite®. The angle between the vertical (cranio-caudal) axis of the face running through the pupil (= vertical midpupillary line) and the direction of the mean skin displacement vector (= mean forehead motion angle) was measured (Figure 2).

2.4 | Statistical analysis

The relationship between the shape of the forehead lines (straight vs. wavy lines) and age, gender, and the mean forehead motion angle was calculated using chi-square test, Student's *t* test, and correlation analyses. All statistical analyses were performed using SPSS Statistics 25 (IBM), and results were considered statistically significant at a level of $P \leq 0.05$ to guide conclusions.

3 | RESULTS

3.1 | General results

Twenty-one (56.8%) volunteers (8 males, 13 females) had straight horizontal forehead lines, whereas 16 (43.2%) volunteers (10 males, six females) had wavy horizontal forehead lines. The mean overall forehead motion angle was 13.19 ± 8.6°, whereas in males the angle was 14.36° ± 8.7 and in females the angle was 12.03° ± 8.4 with no statistically significant difference ($P = 0.250$. Interestingly, females were more frequently observed to display a straight horizontal forehead line type versus males: 68.4% vs 44.4% with $P = 0.037$. Of all volunteers, the mean forehead motion angle on the right side was 13.67° ± 9.5 and on the left side 12.72° ± 7.6 with no statistically significant difference ($P = 0.643$).

3.2 | Relationship between forehead line type and mean forehead motion angle

For volunteers with straight horizontal forehead lines, the mean forehead motion angle was 6.68° ± 2.9 [range: 0.0-12.0], whereas for those with wavy horizontal forehead lines, it was 21.34° ± 5.9 [range: 11.0-37.0] with $P < 0.001$. This statistically significant difference held true when the results were stratified by gender: males straight lines 6.13° ± 2.8 [range: 0.0-11.0] versus wavy 20.95° ± 5.5 [range: 11.0-32.0] ($P < 0.001$); females straight lines 7.04° ± 2.9 [range: 0.0-12.0] vs wavy 22.00° ± 6.6 [range: 11.0-37.0] ($P < 0.001$) (Figure 3).

3.3 | Influence of age on the mean forehead motion angle

Independent of gender, young volunteers (age below 40 years) did not differ in their mean forehead motion angle when compared to older

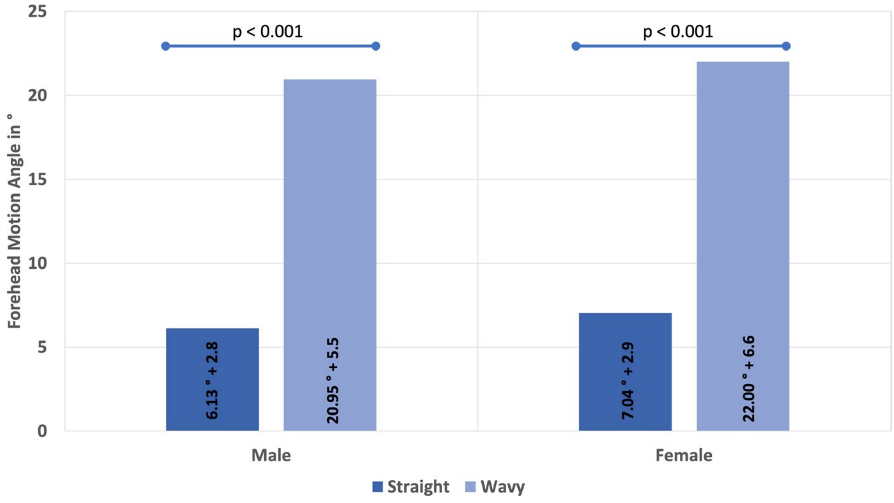

FIGURE 3 Splitted bar graph showing the mean forehead motion angle for males and females with straight forehead lines (dark blue) and wavy forehead lines (light blue). Notice the statistically significant difference of the mean forehead motion angle in individuals with straight and wavy forehead lines ($P < 0.001$ in both, males and females)

volunteers (age above 40 years): males: 14.92° ± 9.2 vs 13.25° ± 7.7 with $P = 0.595$; females: 12.25° ± 8.6 vs 11.75° ± 8.4 with $P = 0.862$. Increasing age was not statistically significantly correlated to a greater mean forehead motion angle with $r_p = -0.104$; $P = 0.386$. This held true when stratifying by gender: males $r_p = -0.030$; $P = 0.861$ and females $r_p = -0.168$; $P = 0.327$.

4 | DISCUSSION

This study was designed to investigate the relationship between forehead skin motion and the shape of the forehead lines utilizing 3D skin vector displacement analysis. Our results revealed that independent of age or gender, a greater forehead motion angle was associated with the presence of wavy forehead lines 21.34° ± 5.9 ($P < 0.001$), whereas straight forehead lines were associated with a smaller forehead motion angle 6.68° ± 2.9 ($P < 0.001$). Additionally, women more frequently exhibited straight horizontal forehead lines when compared to men: 68.4% vs 44.4% ($P = 0.037$). Young volunteers (<39.8 years) did not differ in their mean forehead motion angle vs older volunteers (>39.8 years): 13.70° ± 9.0 vs 12.39° ± 8.0 with $P = 0.530$. No differences were observed between the right and left side of the forehead with $P = 0.944$.

A strength of this study is the standardized measurements and the performed analyses of forehead skin motion utilizing 3D skin vector displacement analyses. The skin vector analyses used the baseline and the follow-up image from the same individual to compute changes in forehead skin position at maximal brow elevation. In this way, interpersonal variation was excluded when calculating individual skin motion. The changes between the baseline and the follow-up images were computed by measuring the difference in corresponding skin features like moles, pores, and other prominent 2-D skin features. This process was standardized across all investigated volunteers and automatically computed by the Vectra Software Suite® to ensure consistency across the investigated population.

The present study expands on the results previously presented by Moqadam et al.[9] In this cadaveric study, published in 2017, the authors investigated in a sample of 31 human body donors the shape of (static) horizontal forehead lines and related their shape to the morphology of the underlying frontalis muscle utilizing cadaveric dissections. The authors reported that the presence of wavy forehead lines versus straight was significantly related to the presence of a midline aponeurosis ($r_p = 0.69$, $P < 0.001$) and was associated with a greater muscle fascicle angle of the frontalis muscle (12.67° ± 2.6 vs 10.18° ± 2.1, $P < 0.001$). A limitation of that study, however, was that the results were obtained from a cadaveric model, and extrapolation to an in vivo clinical scenario could only be postulated. The present study, however, was conducted in healthy volunteers of various age ethnicities, thus potentially bridging the gap between a theoretical cadaveric model and its clinical application in (living) patients.

The results of the present study are consistent with the findings of Moqadam et al.[9] The 3D analyses reveal that wavy horizontal forehead lines are significantly associated with a greater forehead motion angle, whereas straight horizontal forehead lines are associated with a smaller forehead motion angle. Forehead skin motion can be understood as a consequence of a multi-layer soft-tissue response to the underlying muscular contraction. Frontalis muscle contraction is transmitted via short septae also called retinacula cutis to the dermis. This transmission of movement is influenced by the thickness of the superficial subcutaneous fat located inside the three superficial forehead fat compartments,[10] and it can be assumed that a thicker fatty layer results in attenuated skin movement. Likewise, increased septal laxity can result in diminished forehead skin motion due to a reduced force transmission between frontalis muscle and dermis.

Movement of the forehead skin (as a consequence of frontalis muscle contraction) results in the formation of horizontal skin lines (also termed rhytides, or wrinkles). The orientation of those skin lines is perpendicular to the muscle fiber contraction direction forming dynamic lines initially. Dynamic lines are present during muscular contraction only and are absent upon relaxation. Over time, dynamic skin lines might transform into static skin lines which do not disappear upon muscular relaxation.

The results of the present study reveal that the effect of frontalis muscle contraction can present in 2 shapes of horizontal forehead lines: straight or wavy. While a plethora of distinct forehead line patterns has been described, wavy lines have been confirmed in a cadaveric study to be related to a more lateral orientation of the underlying frontalis muscle.[9] This is in contrast to straight horizontal forehead lines which have been related to a more centrally located frontalis muscle.[9]

Utilizing neuromodulators for the treatment of forehead wrinkles results in a temporary paralysis of the underlying frontalis muscle. Incomplete treatment of the frontalis muscle can result in an increased movement of the skin in the areas where the muscle was not affected by the neuromodulator injection.[11-14] If the skin in the lateral aspect of the eyebrow is hyper-elevated during forehead movement following neuromodulator application, the clinical terms "Spock eyebrow" or "Mephisto sign" are used.[15] Based on the results of the present study, it can be assumed that in those cases laterally oriented frontalis muscle fiber are present which were not affected by the (centrally positioned) neuromodulator injection. Individualizing the treatment for forehead neuromodulator applications can account for variations in frontalis muscles morphology and can help avoid aesthetically unappealing outcomes like the "Spock eyebrow" or "Mephisto sign".

Though helpful guides for beginning injectors, neuromodulator injection grid maps providing a 'recipe' for treating all patients should be avoided.[16-21] Customized treatments respecting individual anatomic variation should instead be employed. Based on the findings of this study, the patient should maximally contract the frontalis (ie, maximal brow elevation) to identify if straight or wavy horizontal forehead lines are present. Wavy lines indicate a more lateral location of frontalis muscle fibers, whereas straight lines indicate a more central location of the muscle fibers. Injection points should then be adapted according to the shape of the lines: straight lines more centrally, wavy lines more laterally oriented injection points to help ensure an aesthetically pleasing outcome.

5 | CONCLUSION

The present investigation confirms the findings of a previous cadaveric dissection-based study utilizing 3D skin vector displacement analyses in healthy volunteers. Wavy horizontal forehead lines are associated with are more laterally oriented forehead skin movement, whereas straight horizontal forehead lines are associated with more centrally oriented skin movement. Injections of neuromodulators in the forehead can be individualized by respecting the shape of the horizontal forehead lines. Wavy lines require injection points that are located more laterally, whereas straight lines require more centrally located injection points.

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CONFLICT OF INTEREST

None of the other authors listed have any commercial associations or financial disclosures that might pose or create a conflict of interest with the methods applied or the results presented in this article.

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Publikation 2: Relationship between Forehead Motion and the Shape of Forehead Lines –
A 3–D Skin Displacement Vector Analysis
Englisches – Abstract

Background: Neurotoxin treatments of the forehead region using neuromodulating toxins, though frequently performed, can be challenging. To minimize the number of adverse events practitioners should know the underlying anatomy. A common adverse event of neurotoxin injections in the forehead is eyebrow ptosis. Thus, the aim of this investigation was o investigate differences of the skin movement vectors of the forehead and find a potential explanation for eyebrow ptosis.

Methods: 27 healthy volunteers (11 men and 16 women) with an average age of 37.5 ± 13.7 years (range, 22 to 73 years) and from diverse ethnicities (14 Caucasians, four African Americans, three Asians, and six of Middle Eastern descent) participated in this study. Skin displacement vector analyses was performed during maximal frontalis muscle contraction and during relaxation to assess magnitude and direction of forehead skin vectors.

Results: In 100 percent of scanned participants, a bidirectional movement of the forehead skin was observed: the lower part of the forehead moved in a cranial direction, whereas the upper part of the forehead moved in a caudal direction. Both movements met and converged at a horizontal forehead line which was named line of convergence, or C-line. The position of this C-line was found at 60.9 ± 10.2 percent in men and 60.6 ± 9.6 percent in women ($p = 0.941$) in relation to the entire forehead. Independent of gender, the location of the C-line was found to be at the second horizontal forehead line when counting from cranial to caudal (men, $n = 2$; women, $n = 2$). No differences across ethnicities were detected.

Conclusions: The findings of this study and the discovery of the line of convergence (C-Line) may potentially guide practitioners toward more predictable outcomes when using neurotoxins to ameliorate horizontal forehead lines. Injections above the C-line could mitigate the risk of neuromodulator-induced brow ptosis.

Deutsch – Abstract

Ziel: Die Behandlung der Stirn mit Neurotoxinen gestaltet sich oftmals als Herausforderung. Um Komplikationen und unerwünschte Ergebnisse zu vermeiden, gilt es die zugrundeliegende Anatomie zu verstehen. Klinische lässt sich beobachten, dass Injektionen in die obere Stirn eine Augenbrauenptosis vermeiden können.

Material und Methoden: 27 gesunde Probanden (14 Kaukasier, vier Afroamerikaner, drei Asiaten und sechs aus Mittel-Ost stammende Probanden) mit einem Durchschnittsalter von 37.50 ± 13.7 Jahren [22–73] wurden in dieser Studie untersucht. 3-D-Bilder der Stirn wurden unter Verwendung eines Vectra H1-Kamerasystems angefertigt und analysiert, wobei Orientierung und Größe der Hautverschiebung zwischen der entspannten und der maximal kontrahierten Stirn der Probanden berechnet wurden.

Ergebnisse: In allen untersuchten Probanden (100%) zeigte sich eine bimodale Bewegung des M. frontalis. Die Haut der unteren Stirn bewegte sich nach kranial, wobei die Haut der oberen Stirn sich nach kaudal bewegte. Dieses entgegen gerichteten Bewegungen treffen sich an einer Konvergenzlinie. Welche sich bei 60.9% der relativen Stirnhöhe bei Männern und bei 60.6 % der relativen Stirnhöhe bei Frauen findet.

Schlussfolgerung: Die Identifizierung der Konvergenzlinie (C – Line) könnte in der angewandten Praxis potentiell eine Augenbrauenptosis vermeiden, da die Augenbrauen hebenden Fasern intakt bleiben. Eine Stirnfaltenformation könnte trotz dessen durch Lähmung der oberen Muskelfasern vermieden werden und zu einem ästhetisch ansprechenden Ergebnis führen.

The Bidirectional Movement of the Frontalis Muscle: Introducing the Line of Convergence and Its Potential Clinical Relevance

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Background: Cosmetic treatment of the forehead using neuromodulators is challenging. To avoid adverse events, the underlying anatomy has to be understood and thoughtfully targeted. Clinical observations indicate that eyebrow ptosis can be avoided if neuromodulators are injected in the upper forehead, despite the frontalis muscle being the primary elevator.

Methods: Twenty-seven healthy volunteers (11 men and 16 women) with a mean age of 37.5 ± 13.7 years (range, 22 to 73 years) and of diverse ethnicity (14 Caucasians, four African Americans, three Asians, and six of Middle Eastern descent) were enrolled. Skin displacement vector analyses were conducted on maximal frontalis muscle contraction to calculate magnitude and direction of forehead skin movement.

Results: In 100 percent of investigated volunteers, a bidirectional movement of the forehead skin was observed: the skin of the lower forehead moved cranially, whereas the skin of the upper forehead moved caudally. Both movements converged at a horizontal forehead line termed the line of convergence, or C-line. The position of the C-line relative to the total height of the forehead was 60.9 ± 10.2 percent in men and 60.6 ± 9.6 percent in women ($p = 0.941$). Independent of sex, the C-line was located at the second horizontal forehead line when counting from superior to inferior (men, $n = 2$; women, $n = 2$). No difference across ethnicities was detected.

Conclusions: The identification of the C-line may potentially guide practitioners toward more predictable outcomes for forehead neuromodulator injections. Injections above the C-line could mitigate the risk of neuromodulator-induced brow ptosis. (*Plast. Reconstr. Surg.* 145: 1155, 2020.)

Treating the signs of facial aging has become widely accepted in today's society. Besides soft-tissue filler injections, the administration of facial neuromodulators (i.e., various types of botulinum toxin) to treat facial wrinkles has increased in demand (increase by 845 percent between the years 2000 and 2018 according to the American Society of Plastic Surgeons).[1] Despite the reduced frequency and severity of adverse events when treating the upper face with neuromodulators, the occurrence of eyebrow ptosis and upper eyelid ptosis is undesired and can result in patient dissatisfaction.[2]

The position of the eyebrow needs to be respected, in addition to the shape and the distinctness of horizontal forehead lines (all of those depending on the underlying muscular anatomy). The position of the eyebrow is at a delicate balance between depressors and elevators. Whereas the frontalis muscle is the only elevator, a group of muscles act as depressors: orbicularis oculi, depressor supercilii, corrugator supercilii, and

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procerus muscles. In addition, the morphology of the frontalis muscle and its muscle fascicle angle influence the shape of horizontal forehead lines: a greater muscle fascicle angle that is oriented laterally results in wavy horizontal forehead lines, whereas a smaller and vertically oriented muscle fascicle angle results in straight horizontal forehead lines. Although a helpful guide for less experienced injectors, neuromodulator injection grid maps providing a "recipe" for treating all patients should be avoided.[3–8] Customized treatments respecting individual anatomical variation should instead be used.

The frontalis muscle is considered an eyebrow elevator, and the application of neuromodulators to treat horizontal forehead lines should generally lead to eyebrow ptosis. However, this is inconsistently observed. It is recommended that neurotoxins be applied to the upper forehead instead of the lower forehead to decrease the risk of eyebrow ptosis during treatment.[2] To date, this clinical phenomenon is poorly understood.

The scope of the present analysis was to investigate motion patterns of the skin of the forehead in healthy volunteers during forehead frowning to understand why the application of neuromodulators in the forehead not generally leads to eyebrow ptosis. It is hoped that skin motion patterns can be identified by using vector displacement analyses, which could explain why lower forehead toxin injections carry a greater risk for eyebrow ptosis compared with the upper forehead.

PATIENTS AND METHODS

Study Sample

The sample investigated in the present analysis is a subsample of a study population described previously by Frank et al.[9] The current sample includes 27 healthy volunteers (11 men and 16 women) with a mean age of 37.5 ± 13.7 years (range, 22 to 73 years) and with the following ethnic distribution: 14 Caucasians, four African Americans, three Asians, and six of Middle Eastern descent. Volunteers were excluded from the analysis if previous treatments, operations, or trauma affected the shape and/or the function of the frontalis muscle. In addition, volunteers were excluded from the study if no distinct hairline was present to determine the upper boundary of the forehead. Participants were informed about the aims and procedures of the study. Each participant provided written informed consent for the use of both their data and their associated images. The study was approved by the Institutional Review Board of Ludwig Maximilian University of Munich (protocol number 266-13). This study was conducted in accordance with regional laws (of Germany) and good clinical practice.

Imaging

Three-dimensional images of the full faces of the volunteers were obtained using a Vectra H1 camera system (Canfield Scientific, Inc., Fairfield, N.J.). Baseline and follow-up images were obtained at rest and on maximal forehead frowning. The follow-up image of each participant was automatically aligned to its respective baseline image. Differences in skin position (maximal frowning versus at rest) were computed using skin vector displacement analysis by means of the automated algorithm of the Vectra Software Suite (Figs. 1 through 3).[9] A maximal mean surface deviation of 0.1 mm was tolerated. All measurements were conducted by the same investigator (D.L.F.) to ensure consistency throughout the analyses.

Statistical Analysis

The orientation and the magnitude of forehead skin displacement were recorded and analyzed. Values of skin compression (i.e., reduction in length in percent) and skin displacement (i.e., change in skin position on contraction in millimeters) were calculated based on skin movement. Normal data sample distribution for forehead length, distance of the C-line from the superior orbital rim (absolute and as a percentage), skin compression, and skin displacement were tested by Shapiro-Wilk test and confirmed by means of normality plots and histograms. Differences in values for sexes were calculated using independent sample *t* testing, and results were verified for consistency using the Mann-Whitney *U* test and the bootstrapping method[10,11] because of the small sample size. Differences in values for ethnic subgroups were calculated using analysis of variance testing, and results were verified for consistency using Kruskal-Wallis test and the bootstrapping method. Nonparametric tests were used for calculations on horizontal forehead lines with presentation of the median value and the respective data range (i.e., smallest and greatest values). Differences in skin compression and skin displacement between the region above versus below the C-line were calculated using paired *t* testing and verified by means of the Mann-Whitney *U* test and the bootstrapping method. All statistical analyses were performed using IBM SPSS Version 23 (IBM

Corp., Armonk, N.Y.) and results were considered statistically significant at a level of $p \leq 0.05$ to guide conclusions.

RESULTS

Forehead Length

The mean length of the forehead (i.e., the distance between the upper margin of the eyebrows and the hairline) was 65.0 ± 8.1 mm in men and 53.4 ± 9.2 mm in women ($p = 0.002$). No statistically significant difference in mean forehead length between the four analyzed ethnic groups was identified (unstratified for sex): Caucasian, 57.9 ± 10.3 mm; African American, 58.0 ± 5.1 mm; Asian, 65.7 ± 5.6 mm; and Middle Eastern, 55.0 ± 14.6 mm ($p = 0.565$).

Horizontal Forehead Lines

The median number of observed horizontal forehead lines (irrespective of wavy or straight appearance) was four (range, two to six), which

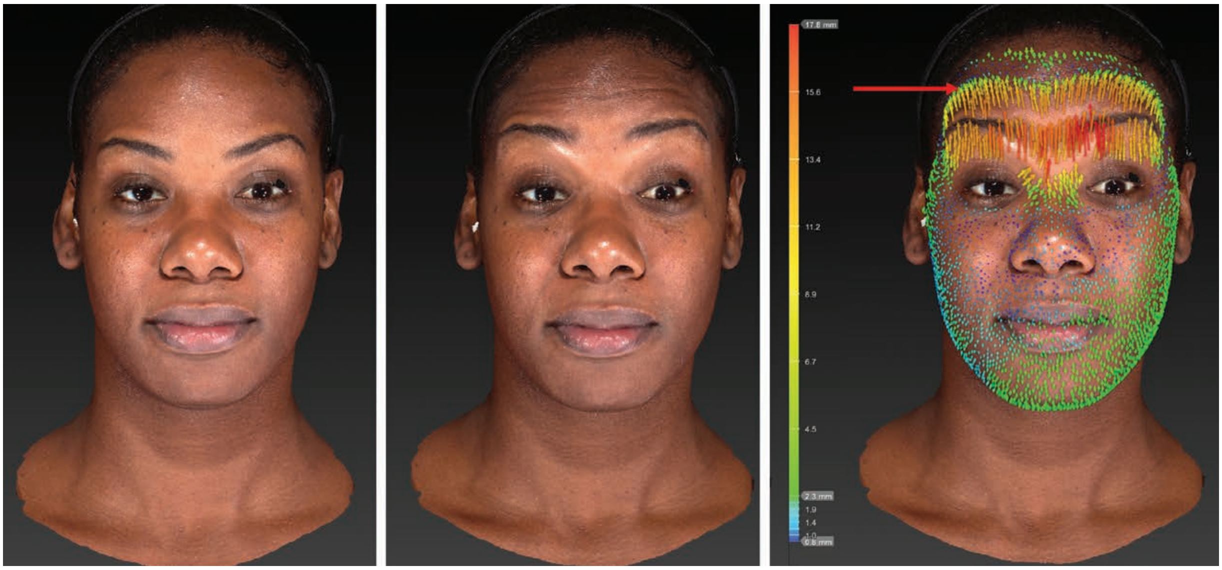

Fig. 1. Processed three-dimensional scan representing the two different states (*left*, resting forehead; *center*, maximal contracted forehead) of the forehead evaluated in this study and their difference in skin displacement represented through vectors (*right*) in a female African American volunteer.

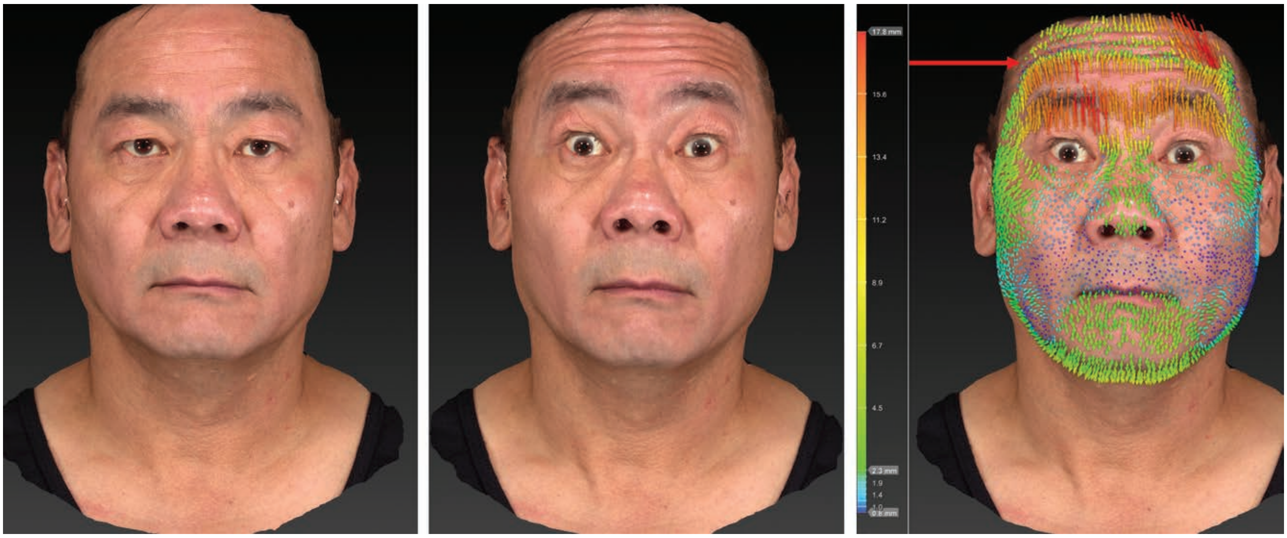

Fig. 2. Processed three-dimensional scan representing the two different states (*left*, resting forehead; *center*, maximal contracted forehead) of the forehead evaluated in this study and their difference in skin displacement represented through vectors (*right*) in a male Asian volunteer.

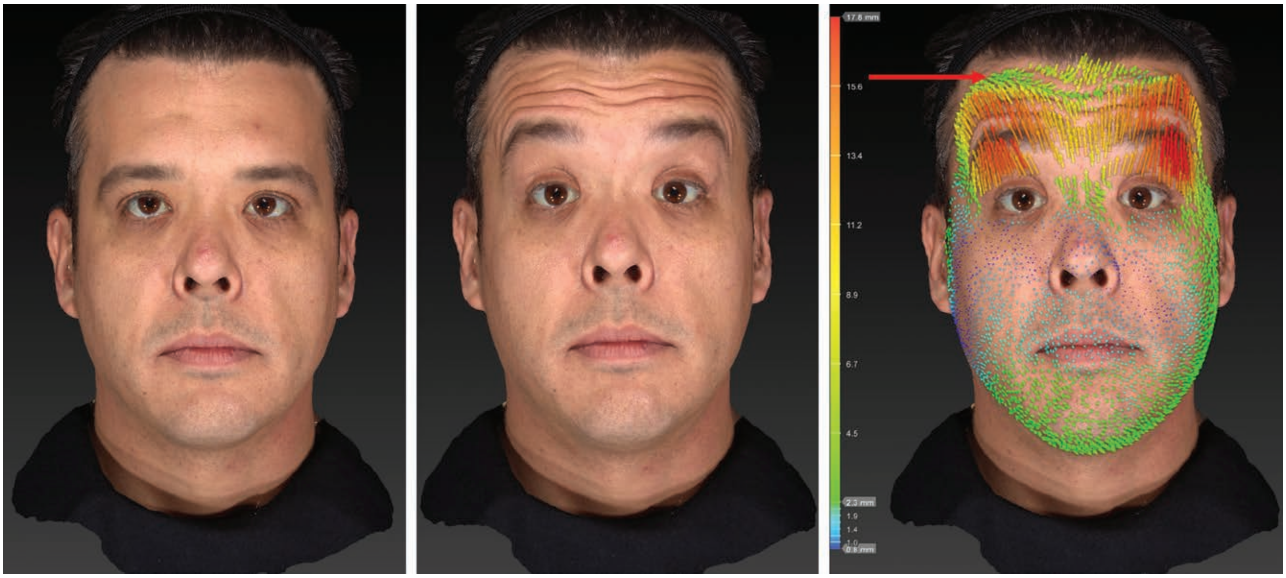

Fig. 3. Processed three-dimensional scan representing the two different states (*left*, resting forehead; *center*, maximal contracted forehead) of the forehead evaluated in this study and their difference in skin displacement represented through vectors (*right*) in a male Caucasian volunteer.

was independent of sex ($p = 0.451$) or ethnicity ($p = 0.148$). There was no statistically significant correlation between the number of horizontal forehead lines and the mean length of the forehead ($r_p = 0.247$; $p = 0.214$).

Line of Convergence

In all investigated volunteers (100 percent), a bimodal movement of the forehead skin was observed, where the skin of the lower forehead moved cranially and the skin of the upper forehead simultaneously moved caudally. This bimodal movement resulted in an elevation of the eyebrows and a depression of the hairline, and an immobile horizontal forehead line where the two movements converged. This stable horizontal forehead line is termed the line of convergence (i.e., C-line).

The C-line was located above the upper margin of the eyebrows at a mean distance of 39.6 ± 7.7 mm in men and 34.3 ± 7.3 mm in women, with no statistically significant difference between sexes ($p = 0.083$). Similarly, no significant difference in the location of the C-line was observed across ethnicities (unstratified for sex): Caucasian, 37.4 ± 7.9 mm; African American, 35.4 ± 7.8 mm; Asian, 41.7 ± 11.4 mm; and Middle Eastern, 32.4 ± 5.3 mm ($p = 0.370$).

The median location of the C-line was at the second horizontal forehead line when counting from the hairline (superior to inferior) irrespective of sex [men, $n = 2.0$ (range, 2.0 to 3.0); women, $n = 2.0$ (range, 1.0 to 3.0); $p = 1.0$]. This was consistent across ethnicities (unstratified for sex): Caucasian, $n = 2.0$; African American, $n = 2.0$; Asian, $n = 2.0$; and Middle Eastern, $n = 2.0$ ($p = 0.731$). The median number of horizontal forehead lines below the C-line was 2.0 (range, 0.0 to 4.0) in men and 2.0 (range, 1.0 to 3.0) in women ($p = 0.394$) and across ethnic groups: Caucasian, $n = 1.0$; African American, $n = 1.0$; Asian, $n = 2.0$; and Middle Eastern, $n = 2.0$ ($p = 0.130$).

The position of the C-line relative to the total height of the forehead was 60.9 ± 10.2 percent in men and 60.6 ± 9.6 percent in women ($p = 0.941$) (Fig. 4). C-line location across ethnicities was (unstratified for sex) as follows: Caucasian, 62.8 ± 8.5 percent; African American, 54.5 ± 10.4 percent; Asian, 61.8 ± 8.6 percent; and Middle Eastern, 59.5 ± 12.6 percent ($p = 0.507$ across groups).

Difference between Upper (above the C-Line) and Lower (below the C-Line) Forehead Parameters

The compression of skin (i.e., reduction in length) in the lower versus the upper forehead was 26.0 percent versus 22.3 percent ($p = 0.089$) in men and 20.9 percent versus 13.7 percent ($p = 0.001$) in women. The gender difference was 5.1 percent ($p = 0.039$) for the lower forehead and 8.5 percent ($p = 0.005$) for the upper forehead (Fig. 5).

The total skin displacement (i.e., change in skin position on maximal frontalis contraction)

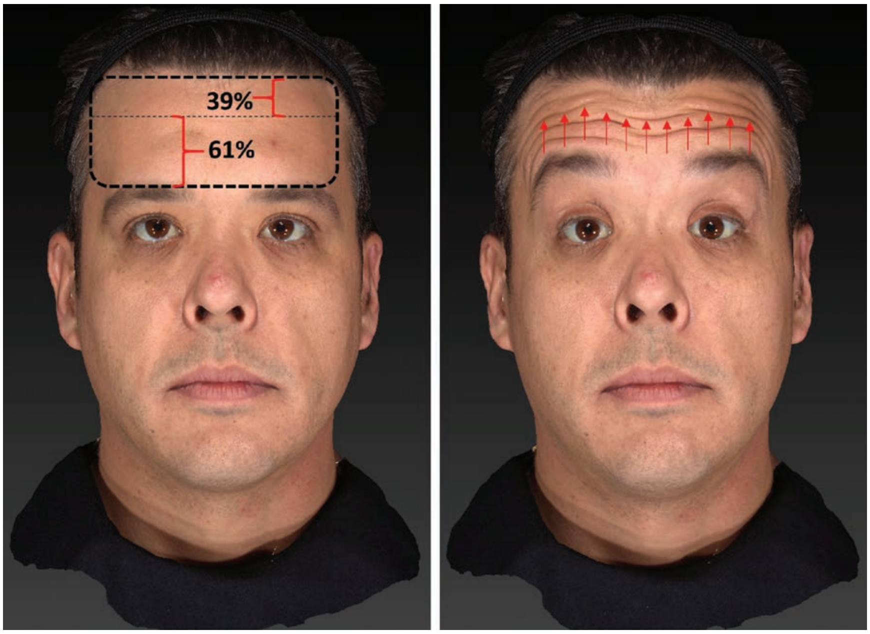

Fig. 4. Processed three-dimensional scan showing the location of the C-line at 61 percent of the mean forehead length (from caudal to cranial) (*left*) and at the second horizontal forehead line (*right*).

was 6.8 mm in men for the upper forehead versus 6.1 mm for the lower forehead (p = 0.244). In women, it was 4.8 mm for the upper forehead versus 3.6 mm for the lower forehead (p = 0.020). The gender difference was 2.5 mm (p = 0.004) for the lower forehead and 2.0 mm (p = 0.001) for the upper forehead (Fig. 6).

DISCUSSION

This skin displacement analysis performed in 27 ethnically diverse individuals for the first time quantifies the bidirectional movement of the skin of the forehead on maximal frontalis muscle contraction: the skin of the lower forehead moves cranially, resulting in an elevation of the eyebrows; whereas the skin of the upper forehead moves caudally, resulting in a depression of the hairline. These two movements meet at a horizontally oriented line termed the line of convergence (C-line). The C-line was located 39.6 ± 7.7 mm above the eyebrows in men and 34.3 ± 7.3 mm in women, which corresponds to 61 percent of the total forehead length in both sexes and was independent of ethnicity (Fig. 4). Interestingly, the C-line was located at the second horizontal forehead line inferior to the hairline independent of sex or ethnicity.

A strength of the present study is that 11 men and 16 women with diverse ethnic backgrounds (Caucasian, African American, Asian, and Middle Eastern) were investigated. This study sample might potentially represent the heterogenous patient population seeking medical intervention in current clinical practice. However, the small overall sample size (n = 27) and the small subsamples in each ethnic subgroup (n = 14 Caucasians, n = 4 African Americans, n = 3 Asians, and n = 6 of Middle Eastern descent) should be regarded as a limitation of the study. A larger sample size with greater numbers, especially in the ethnic subsamples, would have been favorable to strengthen the message presented herein. Future studies with larger samples and/or studies carried out in a clinical scenario will need to expand on the concepts described.

Another strength of this study is the methodology used to measure forehead skin displacement. Three-dimensional skin vector displacement analysis has been shown to provide objective quantification of minute skin movements.[9] This noninvasive, real-time evaluation of skin displacement is based on the mathematical computation of the difference in skin position before and after a movement or intervention. The automated algorithm identifies and tracks the movement of prominent two-dimensional skin features such as moles or skin pores and computes a skin displacement vector. Each vector is characterized by a direction and a specific magnitude. These values can be used to locally and regionally compute skin displacement

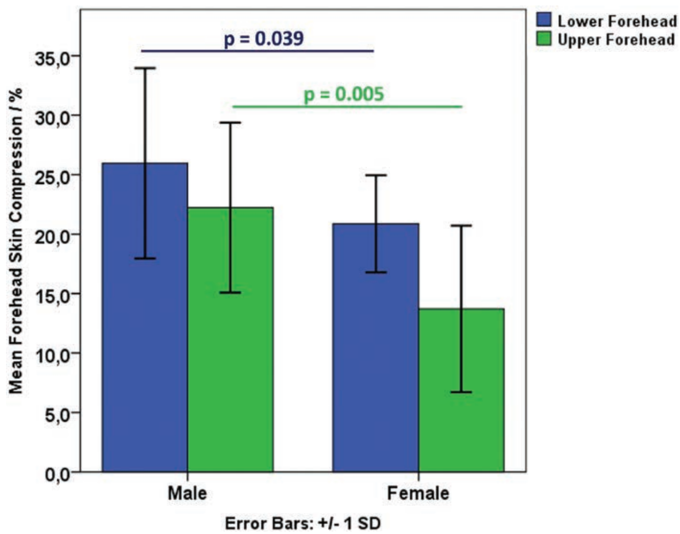

Fig. 5. Bar graph showing the mean forehead skin compression as a percentage for the upper and lower forehead in men and women. Significant differences could be observed between sex for both the upper and the lower forehead ($p = 0.005$ and $p = 0.039$, respectively).

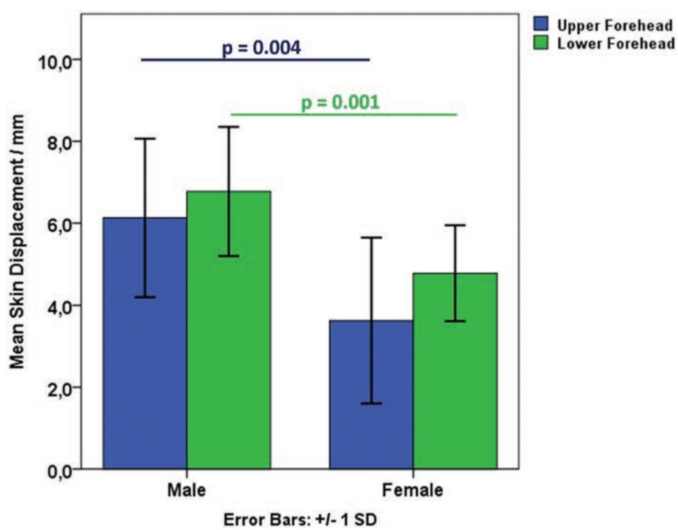

Fig. 6. Bar graph showing the mean skin displacement in millimeters for the upper and lower forehead in men and women. Significant differences could be observed between genders for both the upper and the lower forehead ($p = 0.004$ and $p = 0.001$, respectively).

(change in skin position in millimeters) and skin compression (reduction in length in percent).

In the present analysis, skin vector displacement was used for the total forehead and for the upper versus lower forehead separately. It was found that the skin of the forehead has a bimodal movement. The skin of the lower forehead moved cranially compared with the skin of the upper forehead, which moved caudally. This behavior was observed in 100 percent of the investigated sample. From an anatomical perspective, this is plausible, as the frontalis muscle has no bony origin but is located in its enveloping sheath covered by subcutaneous fat and separated from the deep forehead compartments[12] by the subfrontalis fascia.[13] On contraction of the frontalis muscle, the caudal and the cranial ends are approached, resulting in a bidirectional movement: eyebrow elevation and hairline depression.

Using neuromodulators for the reduction of forehead lines is challenging. The frontalis muscle is the only eyebrow elevator, and its muscle tonus has to be balanced against the eyebrow depressors (i.e., orbicularis oculi, depressor supercilii, corrugator supercilii, and procerus muscles). Reducing frontalis muscle contractility and especially the muscle's eyebrow-elevation segment could result in eyebrow ptosis. This adverse event is transient, and its published incidence ranges from 0.6 to 20 percent. Therefore, injectors should be prepared and openly communicate this potential risk to the patient.[14–16]

Although the present study did not evaluate neuromodulator injections a priori, the results of the present study confirm clinical observations. Injections in the lower forehead can cause eyebrow ptosis, whereas injections in the upper forehead may affect forehead lines but not eyebrow position. Previously published concepts[17] and consensus panel recommendations[18] independently mention that injections within a distance of 2.0 to 3.0 cm above the superior orbital rim increase the risk for eyebrow ptosis. No study to date has provided reliable evidence for this clinical observation and why neuromodulator administration in the lower versus the upper forehead can have different effects on eyebrow position. Our study, however, provides for the first-time reliable evidence, as we were able to show that the frontalis muscle has a bimodal contraction pattern. Whereas the lower part of the muscle acts as an eyebrow elevator, the upper part acts as a hairline depressor. This could explain why injections into the lower part of the muscle (i.e., eyebrow-elevation segment) can result in eyebrow ptosis, whereas injections in the upper part of the muscle (i.e., hairline-depressor segment) do not carry this risk. Decreasing the risk of eyebrow ptosis could be potentially achieved by reducing the units of neuromodulators injected below the C-line versus above it or by repositioning injection points more cranially and focusing more on the C-line region and above. The shape of the (untreated) horizontal forehead lines (straight versus wavy lines)[9,19] might also help to individualize neuromodulator treatment and to guide dosage and injection locations.

Of additional interest, skin compression and skin displacement were significantly increased in men compared with women. This can be understood as the result of the greater frontalis muscle activity caused by increased muscle mass resulting in greater contractility and thus in greater skin movement.[20,21] This larger skin displacement attributable to larger muscle mass is why men often require greater than 50 percent higher neuromodulator dosing than women to achieve a comparable clinical effect.

Future investigations could use skin displacement analysis to study the effects on eyebrow position of neuromodulator injections placed above and below the C-line. It would be especially interesting to determine how successful injections above the C-line with neuromodulator are at smoothing forehead rhytides without causing eyebrow ptosis.

CONCLUSIONS

In this study, a bidirectional movement of the skin of the forehead was observed: the skin of the lower forehead moved cranially, whereas the skin of the upper forehead moved caudally. Both motions met at a static, nonmoving line termed the line of convergence (C-line). The C-line was identified at 61 percent of the total mean forehead length, which was consistent in all sexes and ethnicities. Clinically, the C-line can be identified at the second horizontal forehead line when counting from superior to inferior. Placing neuromodulator injections above the C-line may mitigate the risk of eyebrow ptosis.

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PATIENT CONSENT

Patients provided written consent for the use of their images.

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